Effects of Experimental Right Ventricular Hypertrophy on Myocardial Blood Flow in Conscious Dogs

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ABSTRACT The effects of right ventricular hypertrophy on the overall and regional distribution of myocardial blood flow in the absence of an elevated coronary arterial driving pressure were evaluated in 18 conscious dogs subjected to a chronic pressure overload of the right ventricle induced by pulmonary artery constriction. The sustained pressure overload for duration of 4–6 wk or 4–5 mo resulted in significant increases in right ventricular mass (45 and 110%, respectively) and right ventricular fiber diameter (22 and 60%, respectively). Moreover, the presence of moderate and severe hypertrophy was associated with marked increases in transmural blood flow per gram to the right ventricle proportional to the observed increases in mass, i.e., of 36 and 109%, respectively, from a normal value of 0.67±0.04 ml/min per g, whereas left ventricular blood flow remained unaltered from a normal value of 1.00±0.06 ml/min per g. Despite the large increases in blood flow per gram to moderately and severely hypertrophied right ventricle, no significant changes in the ratio of capillary:muscle fiber number were observed. These data suggest that the development of right ventricular hypertrophy is characterized by a sustained compensatory response of the coronary circulation to the augmented work load and mass, and that it is not associated with a proliferative response of the vasculature supplying the enlarged ventricle.

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INTRODUCTION

One of the primary adjustments to chronic pressure overload involves an increase in myocardial mass, i.e., cardiac hypertrophy. Inadequate perfusion of the hypertrophied ventricle could limit the extent to which the heart can compensate for the pressure overload, and thus may precipitate a decline in ventricular function. Results from recent studies examining the effects of left ventricular hypertrophy on myocardial blood flow appear to be consistent with this hypothesis, in that blood flow per gram of myocardial tissue has been found to be either decreased (1–4), unchanged (5–9), or only slightly elevated (10). This concept is further supported by the observation of Rembert et al. (10), that left ventricular hypertrophy is associated with a relative decline in preferential subendocardial perfusion (i.e., a decrease in the endocardial:epicardial perfusion ratio) at rest.

The changes in myocardial blood flow associated with right ventricular hypertrophy have been examined less extensively (11, 12). Because of the frequent clinical occurrence of right ventricular hypertrophy in response to pulmonary hypertension, as well as congenital pulmonary artery stenosis, it seems important to evaluate both the level and the regional distribution of coronary blood flow associated with chronic, severe, right ventricular hypertrophy in a conscious animal model. Moreover, unlike most currently employed models of left ventricular hypertrophy, where coronary arterial driving pressure is elevated (1–3, 5–10), the experimental model of pressure overload-induced right ventricular hypertrophy is not associated with an elevation in coronary arterial pressure.

The goal of this study, therefore, was to assess the effects of chronic right ventricular pressure overload,

in the absence of an elevated coronary arterial driving pressure, on the magnitude and regional distribution of coronary blood flow to the right ventricle in conscious dogs with either moderate or severe right ventricular hypertrophy, with the nonstimulated left ventricle as an internal control.

METHODS

Instrumentation and induction of right ventricular hypertrophy. 37 mongrel dogs of either sex (conditioned and trained for 1 mo and testing negative for heart worms) were anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated, and artificially ventilated. Through a left thoracotomy in the fourth intercostal space, heparin-filled Tygon catheters (Norton Co., Tallmadge, Ohio) were implanted in the aorta, right ventricle, and left atrium and a hydraulic occluder was placed around the main pulmonary artery. The distal ends of the catheter and occluder were exteriorized and positioned between the scapulae. At least 2 wk were allowed for recovery from the effects of surgery. At this time, 18 of the dogs were subjected to a gradual chronic pressure overload of the right ventricle induced by inflation of the pulmonary artery occluder (13). A stable, peak right ventricular systolic pressure of 50 mm Hg was achieved during the first presentation of the pressure overload. Over the next 2 wk, inflation of the occluder was adjusted such that peak systolic pressure was at least 65 mm Hg, and right ventricular pressure and heart rate were monitored on a weekly basis thereafter. Subsequent changes in right ventricular pressure and all other measured variables occurred spontaneously, and were the result of a consistently applied stenosis of the pulmonary artery. The pressure overload was sustained over a 4- to 6-wk period in 10 of the dogs, whereas the remaining 8 dogs were subjected to the pressure overload for 4–5 mo.

Experimental protocol and measurements. Experiments were performed in a dimly lit, quiet room with the unsedated, conscious dog resting comfortably on its right side. Measurements of aortic and right ventricular systolic and end-diastolic pressures, heart rate, and regional myocardial blood flow were obtained from the normal animals, as well as those with short-term and long-term pressure overload. Aortic and right ventricular systolic and end-diastolic pressures were measured from the previously implanted catheters attached to calibrated strain gauge manometers (Statham P23 Db, Statham Instruments, Inc., Oxnard, Calif.). Mean aortic pressure was obtained with a passive electronic filter with a 2-s time constant. A cardiotachometer (Beckman type 9856, Beckman Instruments, Inc., Fullerton, Calif.), triggered by the arterial pressure pulse, provided instantaneous and continuous records of heart rate. Data were recorded on a multichannel oscillograph (Gould-Brush Inc., Measurement Systems Div., Oxnard, Calif.) and tape recorder (Bell & Howell UR-3700B, Bell & Howell Co., CEC Div., Pasadena, Calif.). Mean coronary vascular resistance was calculated as the quotient of arterial driving pressure (mean aortic pressure minus right ventricular end-diastolic pressure), and the averaged transmural myocardial blood flow for either the right or left ventricle as described below.

Regional myocardial blood flow was measured with carbonized microspheres (7–11 or 13–17 microns in diameter: 3M Co., St. Paul, Minn.) labeled with either ^{51}Cr, ^{85}Sr, ^{141}Ce, or ^{46}Sc. The size and radioactive label of the microsphere was chosen randomly. The microspheres were suspended in 0.01% Tween^{80} solution (10% dextran [Pharmacia Fine Chemicals, Inc., Piscataway, N. J.]) and placed in an ultrasonic bath for 60 min. They were subsequently agitated by direct application of an ultrasonic probe to insure dispersion of the spheres just before injection. Absence of microsphere aggregation was verified by microscopic examination. Before injection of microspheres, 0.7 ml of the Tween^{80}-dextran solution (without microspheres) was injected to determine if the diluent for the microsphere suspension was to have an adverse effect on cardiac dynamics (14). 1- to 2 million microspheres, suspended in 10% dextran, were injected through the catheter implanted in the left atrium for determination of blood flow. A reference sample of arterial blood was withdrawn, beginning 10 s before microsphere injection and continuing for 40 s after the injection was completed (total withdrawal time 90 s). Multiple determinations of myocardial blood flow were obtained in each animal. In the animals with long-term pressure overload, injections were also made 1–2 wk apart before sacrifice to confirm the stability of the observed flow measurements. None of the animals used in this study exhibited exercise intolerance, and no thoracic or abdominal ascites or pronounced hepatic congestion was found on postmortem examination, which indicates that these animals were not in congestive heart failure. After sacrifice of the animal, the heart was excised, and the atria, great vessels, valves, large surface vessels, and epicardial fat were discarded. The free wall of the right ventricle and the left ventricle (including septum) were weighed separately. Values for ventricular mass:body weight ratio were computed with the body weight of the dog at the time of surgery. Right ventricular wall thickness was measured at a consistent site in the mid-free wall and included trabeculae muscles. The free wall of the right ventricle was divided equally into eight regional segments, the position of each segment being consistent from dog to dog. A sample from each regional segment in turn was divided into endocardial and epicardial layers and weighed. Six transmural samples were also taken from the left ventricular free wall between the anterior and posterior papillary muscles and divided into endocardial and epicardial layers and weighed. In general, the weights of these myocardial samples ranged between 0.7 and 1.5 g. The samples were then placed in a multichannel gamma well counter (Searle Analytic Co., subsid. of G. D. Searle & Co., Des Plaines, Ill.), and counted with appropriately selected energy windows for 10 min. The raw counts were corrected for background and crossover and compared with the reference blood sample to obtain flow expressed in milliliters per minute per gram of tissue. The values reported for right and left ventricular flow per gram of tissue represent the weighted average of all segments from the respective ventricle of a given dog. The multiple determinations of flow were averaged before inclusion in the final data pool, so that all dogs were weighted equally. Myocardial blood flow measurements were made only in those long-term pressure overload dogs where the left atrial catheter remained patent for the 4- to 5-mo period (4 of 8).

The capillary:muscle fiber number ratio for both the right and left ventricles of normal and long-term pressure overload animals was determined with histologic techniques described previously (15–17). Histologic sections from heart perfused post-mortem with formalin and black ink at 100 mm Hg pressure were examined at a magnification of 400. A 10 × 10-mm calibrated microscope eyepiece grid was used to delineate areas used for counting. All counts were made on fields in which fibers and capillaries appeared predominantly circular (rather than cylindrical or ellipsoidal), which indicates that they were cut transversely. Thus, only true cross-sections were counted. Areas in which the capillaries were not well delineated with ink were excluded from the study.

A total of 200 fibers and capillaries were counted from each ventricle. Myocardial fiber diameters, 20 from each ventricle, were measured at a magnification of 1,000 with the calibrated eyepiece grid in normal, short-term and long-term pressure overload groups. The histological samples were analyzed independently by a pathologist, who had no prior notification of the group classification of the sample.

Data analysis. All experiments were performed on conscious dogs that were divided into three separate groups (normal; short-term pressure overload [4–6 wk]; and long-term pressure overload [4–5 mol]). Differences between the normal and short-term pressure overload group, normal and long-term pressure overload group, and short- and long-term pressure overload groups were tested for statistical significance by analysis of variance and the Scheffe test (18). Data presented represent mean±SEM values.

RESULTS

Morphometric characteristics (Table I). The morphometric characteristics of normal dogs, and dogs subjected to either 4–6 wk or 4–5 mo of right ventricular pressure overload, are presented in Table I. No significant differences in left ventricular weight:body weight ratio were evident among the three groups. In marked contrast, right ventricular weight:body weight ratio was substantially elevated ($P < 0.01$) after 4–6 wk of pressure overload to 2.07±0.09 g/kg from a normal value of 1.43±0.06, and further increased ($P < 0.01$) to 3.01±0.23 after 4–5 mo of pressure overload. Right ventricular wall thickness increased ($P < 0.01$) from 5.56±0.13 mm to 9.83±0.41 and 11.25±0.88 with short- and long-term pressure overload, respectively. Right ventricular:left ventricular weight ratio increased ($P < 0.01$) to 0.44±0.02 after 4–6 wk of pressure overload from a normal value of 0.29±0.01, and was further elevated ($P < 0.01$) to 0.63±0.04 after 4–5 mo of pressure overload. Left ventricular fiber diameter remained unchanged after 4–6 wk of pressure overload at 11.18 ±0.39 microns from a normal value of 11.61±0.62, but was increased ($P < 0.01$) to 15.49±0.64 after 4–5 mo of pressure overload. Right ventricular fiber diameter was increased ($P < 0.05$) to 13.83±0.86 microns from a normal value of 11.34±0.67 after short-term pressure overload, and was further elevated ($P < 0.01$) to 18.16 ±0.79 after long-term pressure overload. Whereas normal values of right and left ventricular fiber diameter were not significantly different, the increases in right ventricular fiber diameter associated with both short- and long-term pressure overload were significantly greater ($P < 0.02$) than the concomitant changes in left ventricular fiber diameter. The capillary:muscle fiber number ratio in both the right and left ventricles remained unchanged after 4–5 mo of pressure overload.

Hemodynamic characteristics (Table II). The hemodynamic status of normal, moderate, and severely hypertrophied groups in terms of mean aortic pressure, heart rate, right ventricular systolic pressure, and right ventricular end-diastolic pressure is presented in Table II. Whereas there were no significant differences in mean aortic pressure among the three groups, a small increase ($P < 0.01$) in heart rate to 103±7 beats/min from a normal value of 82±3 was observed after 4–6 wk of pressure overload, but not after 4–5 mo of pressure overload (95±6). Right ventricular systolic pressure was progressively increased ($P < 0.01$) to 78±3 mm Hg after 4–6 wk of pressure overload and further elevated ($P < 0.05$) to 102±9 after 4–5 mo of pressure overload from a normal value of 31±4. Right ventricular end-diastolic pressure was increased ($P < 0.01$) to 6.7±0.6 and 8.5±0.7 mm Hg with short- and long-term pressure overload, respectively, from a normal value of 4.2±0.3.

Myocardial blood flow (Table III). The changes in myocardial blood flow associated with the development of moderate and severe right ventricular hyper-

TABLE I
Morphometric Characteristics of Right Ventricular Hypertrophy

	Normal	Hypertrophied (4–6 wk)	Hypertrophied (4–5 mo)
LV weight/body weight, *g/kg*	4.95±0.18	4.81±0.21	4.66±0.36
RV weight/body weight, *g/kg*	1.43±0.06	2.07±0.09‡	3.01±0.23‡§
RV thickness,* *mm*	5.56±0.13	9.83±0.41‡	11.25±0.88‡
RV weight/LV weight	0.29±0.01	0.44±0.02‡	0.63±0.04‡§
RV fiber diameter, *microns*	11.34±0.67	13.83±0.86‖	18.16±0.79‡§
LV fiber diameter, *microns*	11.61±0.62	11.18±0.39	15.49±0.64‡§
RV capillary number/fiber number	0.836±0.03	—	0.846±0.01
LV capillary number/fiber number	0.834±0.01	—	0.850±0.01

LV, left ventricular; RV, right ventricular.
* RV thickness measured in the mid-free wall (including trabeculae) in all animals.
‡ Represents difference ($P < 0.01$) from normal group.
§ Represents difference ($P < 0.01$) from hypertrophy group (4–6 wk).
‖ Represents difference ($P < 0.05$) from normal group.

TABLE II
Hemodynamic Characteristics of Right Ventricular Hypertrophy

	Normal	Hypertrophied (4–6 wk)	Hypertrophied (4–5 mo)
Mean aortic pressure, *mm Hg*	97±2	99±4	90±3
Heart rate, *beats/min*	82±3	103±7*	95±6
RV systolic pressure, *mm Hg*	31±4	78±3*	102±9*‡
RV end-diastolic pressure, *mm Hg*	4.2±0.3	6.7±0.6*	8.5±0.7*

RV, right ventricular.
* Represents difference ($P < 0.01$) from normal group.
‡ Represents difference ($P < 0.05$) from hypertrophy group (4–6 wk).

trophy are presented in Table III. It should be noted that blood flow per gram in the normal right ventricle, 0.67±0.04 ml/min per g, was significantly less ($P < 0.01$) than that of the normal left ventricle, 1.00±0.06 ml/min per g. There were no significant differences in left ventricular blood flow among the three groups. In contrast, the development of right ventricular hypertrophy induced by short-term pressure overload was associated with a significant ($P < 0.05$) increase in transmural blood flow to the right ventricle of 36%. Right ventricular blood flow rose further ($P < 0.05$), to 109% above normal levels, after 4–5 mo of pressure overload. In three of the dogs subjected to 4–5 mo of pressure overload, a second separate determination of blood flow after a 1-wk interval indicated that the observed increases in blood flow to the hypertrophied right ventricle were stable (1.40±0.20 vs. 1.53±0.34 ml/min per g for the first and second determinations of blood flow, respectively).

Changes in calculated coronary vascular resistance associated with the development of right ventricular hypertrophy followed a similar but reciprocal pattern. Whereas calculated resistance decreased ($P < 0.01$) by 32% from a normal value of 147±8 mm Hg/ml per min per g with right ventricular hypertrophy induced by short-term pressure overload, and was further decreased ($P < 0.05$) to 57% below normal with long-term pressure overload, no significant changes in resistance for the left ventricle were noted among the three groups.

DISCUSSION

The results of this study clearly indicate that this experimental model of right ventricular pressure overload induced via pulmonary artery constriction is associated with very substantial hypertrophy of the right ventricle. Whereas significant hypertrophy is evi-

TABLE III
Effects of Right Ventricular Hypertrophy on Overall and Regional Distribution of Myocardial Blood Flow

	Normal	Hypertrophied (4–6 wk)	Hypertrophied (4–5 mo)
Left ventricle			
Transmural flow, *ml/min/g*	1.00±0.06	1.01±0.09	1.00±0.19
Calculated resistance, *mm Hg/ml/min/g*	102±6	103±12	85±8
Endo/epi	1.17±0.03	1.23±0.07	1.31±0.14
Right ventricle			
Transmural flow, *ml/min/g*	0.67±0.04	0.91±0.07*	1.40±0.23*‡
Calculated resistance, *mm Hg/ml/min/g*	147±8	100±10§	63±9‡§
Endo/epi	1.17±0.04	1.10±0.05	1.14±0.03

Endo/epi, endocardial:epicardial perfusion ratios.
* Represents difference ($P < 0.05$) from normal group.
‡ Represents difference ($P < 0.05$) from hypertrophy group (4–6 wk).
§ Represents difference ($P < 0.01$) from normal group.

dent after 4–6 wk of pressure overload, further increases in both right ventricular weight:body weight ratio, right ventricular weight:left ventricular weight ratio, and right ventricular fiber diameter were observed after 4–5 mo of pressure overload. The major finding of this investigation, however, is that in contrast to the reported results with the development of left ventricular hypertrophy (1–10), the development of right ventricular hypertrophy is characterized by marked increases in right ventricular transmural myocardial blood flow and decreases in resistance across the right coronary bed. The further enhancement in blood flow to the hypertrophied right ventricle after 4–5 mo of pressure overload suggests that the observed elevations in blood flow are not a transient phenomenon, but rather a sustained compensatory response to the pressure overload.

The level of coronary blood flow is primarily determined by five main factors; (*a*) coronary perfusion pressure; (*b*) myocardial systolic compression; (*c*) neurohumoral factors; (*d*) vascular density; and (*e*) myocardial oxygen consumption. The observed increases in myocardial blood flow to the hypertrophied right ventricle cannot be the result of an increase in coronary perfusion pressure, because coronary perfusion pressure decreased in the face of a constant aortic pressure and an increasing right ventricular end-diastolic pressure. Nor is it likely that the elevated coronary blood flow levels are the result of a diminution of systolic myocardial compressive forces, because, as illustrated in Fig. 1, this experimental model of severe right ventricular hypertrophy is actually characterized by a decrease in systolic right coronary flow, with the phasic right coronary flow pattern of the severely hypertrophied right ventricle bearing a striking resemblance to the normal phasic flow pattern of the left circumflex coronary artery. This observation was also made by Lowensohn et al (11), while examining the effects of congenital pulmonary artery stenosis on right coronary artery flow in conscious dogs. Whereas direct neural or humoral control of the coronary vasculature cannot be ruled out as being responsible for the observed increases in blood flow, this result would be surprising because the increase in blood flow was unique to the right ventricle. Because no alteration in the capillary: muscle fiber number ratio was observed in the severely hypertrophied right ventricle, it appears that an increase in vascular density cannot be responsible for the observed increases in blood flow. Therefore, it appears that increases in blood flow to the hypertrophied right ventricle are most likely a result of increases in right ventricular metabolic requirements. This preparation does not permit sampling of the venous effluent from the hypertrophied right ventricle, thus direct measurements of right ventricular oxygen consumption are not possible. However, heart rate, ventricular wall tension, contractility, and afterload

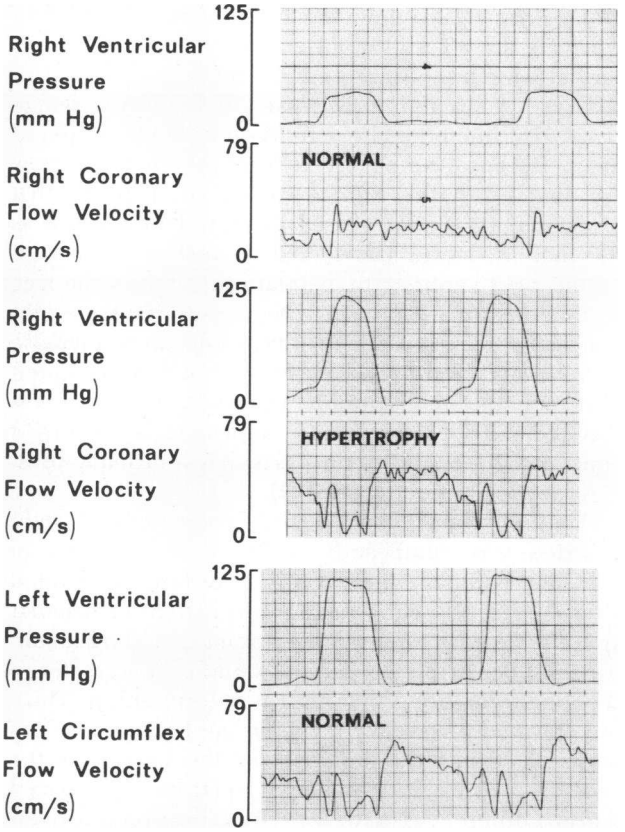

FIGURE 1 Phasic ventricular pressure and coronary flow velocity obtained from conscious dogs with normal right ventricle (top panel), hypertrophied right ventricle induced by 5 mo of pulmonary artery stenosis (middle panel), and normal left ventricle (bottom panel). Ventricular pressures were measured with an implanted catheter (hypertrophied right ventricle) or a miniature solid state pressure transducer (Konigsberg P22 [Konigsberg Instruments, Inc., Pasadena, Calif.]) implanted in normal right or left ventricles and calibrated both in vitro and in vivo with implanted right ventricular, aortic, and left atrial catheters attached to Statham P23 Db strain gauge manometers. Coronary blood flow velocity was measured with the nondirectional CW Doppler ultrasonic flowmeter. The blood flow transducers were placed around the main right coronary artery or the circumflex branch of the left main coronary artery. Note the sharp reduction in systolic right coronary flow, as a proportion of total coronary flow in the severely hypertrophied right ventricle, as contrasted with the normal right ventricle. It can also be seen that the phasic coronary flow pattern of the hypertrophied right ventricle closely resembles the phasic coronary flow pattern in the normal left ventricle.

are all important determinants of myocardial oxygen consumption. Whereas heart rate was slightly elevated after 4–6 wk of pressure overload, it was not significantly different from normal levels after 4–5 mo of pressure overload, which makes it very unlikely that this factor contributed to the observed increases in blood flow. It is also unlikely that the observed in-

creases in blood flow to the hypertrophied right ventricle are a result of an enhancement of the myocardial contractile state because most studies to date have reported either a decrease (19, 20) or no change (1, 21–23) in contractile activity of the hypertrophied heart. Because the observed increases in blood flow are specific to the right ventricle, it is likely that a major determinant of this increased blood flow is the increased external work that must be performed by the right ventricle to maintain function in the face of the pressure overload. The possibility that right ventricular hypertension results in a sustained increase in ventricular wall tension that is not fully compensated by the hypertrophic process cannot be discounted. This finding would appear to be in direct contrast to the results of studies on left ventricular pressure overload hypertrophy (21).

Whereas blood flow to the hypertrophied right ventricle was significantly increased after 4–6 wk of pressure overload, these levels were further elevated after 4–5 mo of overload. Moreover, right ventricular systolic pressure, right ventricular mass, and right ventricular fiber diameter were all significantly greater in the long-term group than the short-term group. Thus, the elevated blood flow levels in the long-term group may reflect both the duration and the severity of the pressure overload. However, it must be emphasized that any differences in the severity of the pressure overload occurred spontaneously and were not the result of a further application of the pressure overload stimulus.

In addition to the differences in the ventricle being stressed, one other major difference between prior studies on left ventricular hypertrophy (1–3, 5–10) and this investigation deserves mention. Most currently employed models of left ventricular hypertrophy are associated with an elevated coronary arterial driving pressure. It is possible that this elevated pressure elicits morphologic changes in the coronary vascular anatomy, which in turn could limit the magnitude of a compensatory flow response. Indeed, Dowell (24) has reported that left ventricular hypertrophy induced by aortic stenosis is associated with a decrease in the vascular denisty of the left ventricular myocardium. Further support for this hypothesis comes from a recent study by O'Keefe et al. (5), which reports that moderate left ventricular hypertrophy induced by aortic stenosis is associated with a thickening of the vascular wall of coronary vessels that supply the hypertrophied ventricle. Whereas a reduction in vascular density could act to limit compensatory vasodilation with the development of left ventricular hypertrophy, the increases in right ventricular blood flow observed in this study appear not to be the result of an increase in vascular density of the hypertrophied right ventricle because the capillary:muscle fiber number ratio was unchanged after 4–5 mo of pressure overload.

Whereas the observed effects of right ventricular hypertrophy on myocardial blood flow are not totally dissimilar from those reported by Archie et al. (12), several important differences do exist. First, in our study, right ventricular hypertrophy is associated with significant and selective increases in right ventricular flow per gram, i.e., no change in left ventricular flow per gram occurred, as contrasted with statistically insignificant increases in both right and left ventricular flow as reported by Archie et al. (12). Second, to avoid the marked direct and indirect effects of anesthesia on myocardial function and blood flow (25), our experiments were performed on fully conscious dogs, whereas Archie et al. (12) employed sedated animal preparations. And third, in our study, the pressure overload-induced hypertrophy was produced in adult, fully developed dogs, subjected to both short- and long-term pressure overload, whereas Archie et al. (12), banded the pulmonary artery of 2-d-old lambs and subsequently studied the effects of the pressure overload 5-12 wk later. Whereas in the adult animal, the increase in right ventricular mass is thought to be primarily a result of an increase in cell size but not cell number (26, 27), in the newborn, both hypertrophy and hyperplasia may account for the increase in ventricular mass. In the adult experimental model of right ventricular hypertrophy used in this study, we observed a progressive increase in right ventricular fiber diameter with both short- and long-term pressure overload. Changes in fiber diameter were not reported in the study by Archie et al. (12). Thus, the specific effects of the pressure overload on myocardial blood flow in the developing lamb and the adult dog could well be mediated through different mechanisms.

In conclusion, these data indicate that chronic pressure overload of the right ventricle in the conscious dog of 4- to 6-wk duration is associated with significant hypertrophy of the right, but not the left, ventricle, with even more marked right ventricular hypertrophy after 4–5 mo of pressure overload. In contrast with previously reported changes in myocardial blood flow per gram of hypertrophied left ventricle (1–10), the development of right ventricular hypertrophy was characterized by substantial and specific increases in blood flow per gram of right ventricle, which were even more marked after 4–5 mo of pressure overload.

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